Enantioselective copper catalyzed allylic alkylation using Grignard reagents; Applications in synthesis

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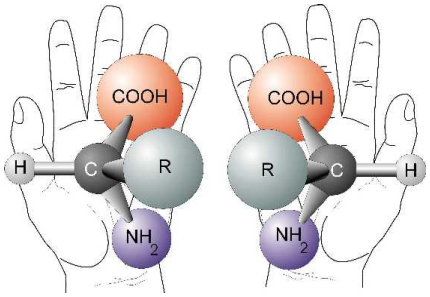
English Summary

The main focus of research in the field of synthetic organic chemistry is on the development of new methods for preparing organic compounds. Organic compounds consist of atoms from the elements carbon (C) and hydrogen (H) and in addition regularly contain several heteroatoms.* As a result, organic molecules are built up from a relatively small number of elements. Nevertheless, an impressive number of natural and non-natural organic compounds are known to us and an even greater number can still be discovered or synthesized. These compounds differ from each other in the number of atoms, in the bonds between these atoms and in the spatial orientation of these bonds.



Chirality (derived from Greek, χειρ = hand) is the property of an object in which the mirror images are non-superimposable. In organic chemistry this signifies that the two mirror images of a chiral compound, *enantiomers*, are equal in every aspect except the absolute spatial orientation of the bonds, which is exactly opposite. This is the case, when a carbon atom is bound to four different groups that surround it like a tetrahedron. The two enantiomers of, for example, an amino acid differ in no other way than the fact that they are mirror images of each other. It is the same with, for example, a left and a right hand (see figure in text). The physical and chemical properties of two enantiomers are exactly the same, except in the interaction with other chiral compounds.

In our bodies almost all our receptors and enzymes are chiral, also. As a result, their interaction with a biologically active chiral compound, such as a medicinal drug, is often different for the two enantiomers of this compound. Hence it is of importance for the pharmaceutical industry, among others, to have access to methods for obtaining one of the two enantiomers in a pure state. Several methods are available to achieve this goal. Amongst these methods asymmetric catalysis, the subject of this thesis, is a particularly powerful and efficient one.

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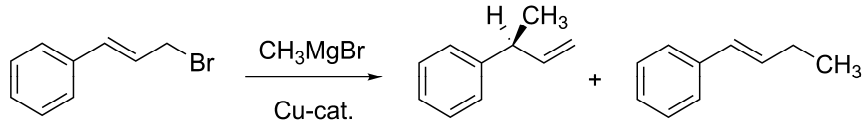
* Heteroatoms in organic compounds are atoms from a select number of other elements, such as, for example, oxygen (O), nitrogen (N) and sulfur (S).

A catalyst is a compound that accelerates a reaction without, overall, being altered by the process. This allows a small amount of catalyst to transform a larger amount of substrate into the desired product. A chiral catalyst can be used to convert an achiral substrate selectively into one of the two enantiomers of a chiral product. The chemical reaction that is the main subject of this thesis is the allylic alkylation (Scheme 1, black lines represent carbon atoms and their bonds; most hydrogen atoms are omitted for clarity; the arrow indicates the direction of the reaction).



Scheme 1: An enantioselective copper catalyzed allylic alkylation involving a Grignard reagent.

The allylic alkylation proceeds by reaction of an allyl bromide as a substrate (left of the arrow) with an alkylmagnesium reagent, a so-called *Grignard* reagent (above the arrow). The bromine atom (Br) of the substrate is replaced with the alkyl group of the Grignard reagent (in Scheme 1 this is a CH_3). The two possible products are seen right of the arrow. Both products have had the bromine atom replaced; however, the CH_3 group can be bound to two distinct carbon atoms of the substrate. The catalyst that is used for this reaction is a complex of a copper atom (Cu) with a chiral *ligand*, an organic compound surrounding the copper atom.

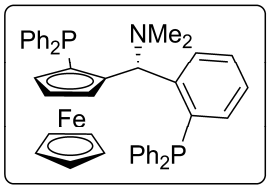
Scheme 1 shows that the product on the left contains a carbon atom bound to four different groups.[†] This is the desired chiral product. A good catalyst needs to be both regioselective (producing selectively the chiral product and not the undesired product on the right) and enantioselective (producing selectively one of the two enantiomers of the chiral product).[‡] This thesis describes the development of a new catalyst for this reaction and its use in the synthesis of relevant organic compounds.

[†] In three dimensions, one must envision the bold line (to the CH_3) to be standing towards the reader and the hashed line (to the H) to be standing away from the reader.

[‡] These selectivities are expressed in the relative percentages of the two distinct products (regioselectivity) and of the two enantiomers of the chiral product (enantioselectivity).

Chapter 1

A short introduction to asymmetric catalysis is provided in chapter 1. In addition this chapter contains an overview of catalytic enantioselective substitution reactions. This overview gives a general indication of the possibilities of the use of catalysts based on metals other than copper. Subsequently, a review is provided of the results obtained by our group and others in the copper catalyzed version of the reaction and an explanation is given for why copper occupies a specific niche compared to the other catalytic metals.

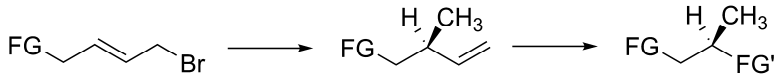


Chapter 2

In chapter 2 the development of the new catalyst is described. This chiral catalyst is based on copper and the ligand Taniaphos (see figure in text), which binds to copper with two phosphorus atoms (P). The yield of the reaction (>90%), as well as the regioselectivity (the ratio of the products is 97:3) and the enantioselectivity (the ratio of the two enantiomers is 99:1) are high. Especially the introduction of a CH_3 group proceeds with excellent selectivity. This is important, because it is a common motif in biologically active compounds and because it was difficult to introduce the CH_3 group through allylic alkylation using the catalysts reported previously.

Chapter 3

A functional group is a part of a molecule, on which reactions can be performed. Because the product of an enantioselective reaction usually is not the final target molecule, it is important that this product has sufficient functional groups to synthesize this target molecule through subsequent reactions. In chapter 3 the application in the allylic alkylation of substrates with an extra functional group is described (Scheme 2, the first arrow indicates the allylic alkylation). This extra functional group is

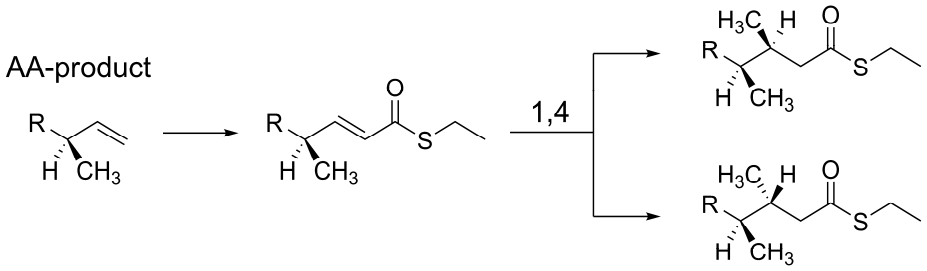


Scheme 2: The synthesis in two steps of relevant building blocks containing two distinct functional groups (FG and FG') through copper catalyzed allylic alkylation (step one) and several subsequent reactions (step two).

retained in the product. In subsequent reactions the products are transformed into building blocks containing two functional groups (the second arrow indicates the subsequent reaction). These versatile building blocks are applicable in the synthesis of relevant compounds, such as pharmaceuticals.

Chapter 4

In chapter 4 the combination of the copper catalyzed allylic alkylation and 1,4-addition is discussed. The 1,4-addition is a copper catalyzed enantioselective reaction, also and is somewhat similar to the allylic alkylation. It is important to know that the products of an allylic alkylation can be transformed (Scheme 3, first step) into molecules that can function as a substrate in an enantioselective 1,4-addition. Subsequently, the 1,4-addition introduces a second CH_3 group (Scheme 3, second step).

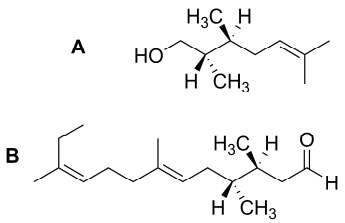


Scheme 3: After a single transformation (step one), the products of an allylic alkylation can be applied as substrates in a 1,4-addition (step two); R is a non-specified group.

Through this combination of allylic alkylation and 1,4-addition a product is obtained that contains two adjacent carbon atoms, which are both bound to four different groups. In this case four distinct products are possible (the two products in scheme 3 and their enantiomers). The choice of the enantiomer of the catalyst in the allylic alkylation directs the configuration of the first carbon atom and the choice of the enantiomer of the catalyst in the 1,4-addition directs the configuration of the second carbon atom. Because of this the new route allows for the preparation of each of these four possible products in a selective fashion.

Such a route can be useful in the synthesis of biologically active compounds. To demonstrate that this is a real possibility, the route was

applied in the synthesis of two pheromones of two species of ants. Both pheromones, lasiol (**A**) and faranal (B) contain the same structural element: two adjacent carbon atoms, both with a CH_3 group bound to it (see figure in text).

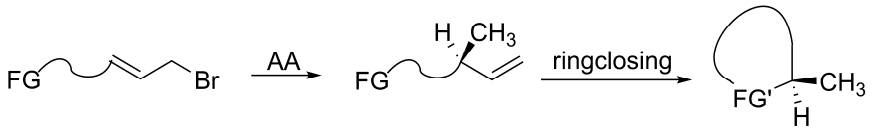


Chapter 5

The route described in chapter 4 contains a reaction, which transforms the product of an allylic alkylation into a substrate for a 1,4-addition. This reaction is called cross-metathesis. The best results in the 1,4-addition were obtained with specific sulfur containing substrates, *thioesters*. However, these thioesters had not been prepared before using cross-metathesis. In chapter 5 the possibilities of the use of cross-metathesis in the synthesis of these thioesters are explored.

Chapter 6

In chapter 6 the use of the copper catalyzed allylic alkylation in the synthesis of *heterocyclic* compounds is described.[§] Many biologically active compounds contain heterocycles. The substrates used in chapter 6 contain an extra functional group. After the allylic alkylation (Scheme 4, step one), this functional group is used in a subsequent reaction (Scheme 4, step two) to close the ring and form the heterocycle.



Scheme 4: The application of the copper catalyzed allylic alkylation in the synthesis of heterocyclic compounds. The wavy line is a non-specified chain of carbon and heteroatoms.

[§] Heterocycles are molecules of which the bonds between the atoms form a ring that contains at least one heteroatom also (*e.g.* oxygen or nitrogen).

Conclusions

In this thesis the development of a new catalyst for enantioselective copper catalyzed allylic alkylation is described. The high regio- and enantioselectivity of the new catalyst, in particular with the introduction of a CH_3 group, makes the catalyst complementary to the catalysts reported previously for this reaction.

In addition, the enantioselective copper catalyzed allylic alkylation was applied in the synthesis of relevant organic compounds, such as building blocks containing two functional groups, pheromones and heterocyclic compounds. This demonstrates that this reaction can make a valuable contribution to the possibilities that synthetic organic chemists have. In part due to this work, they might decide on applying asymmetric catalytic methods instead of older less efficient methods, when they wish to synthesize chiral compounds, such as for instance medicinal compounds.